1.3.1 Prescribing Information (Summary of product characteristics)

1. Name of the medicinal product:

Tizanidine Tablets USP 2 mg

2. Qualitative and quantitative composition

Sr. No.	Name of Ingredient	Specification	Quantity per Tablet (mg)	% Overages	Reason for inclusion
DRY MIXING					
1.	Microcrystalline cellulose	BP	159.683**	–	Diluent
2.	Sodium starch glycolate	BP	4.000	–	Disintegrant
BINDER SOLUTION					
3.	Colour Quinoline Yellow (SUPRA)	IHS	0.030	–	Colouring agent
4.	Purified water	BP	q.s.	–	Solvent
BLENDING					
5.	Tizanidine HCL	USP	2.287*	–	Active
6.	Crospovidone	BP	6.000	–	Disintegrant
7.	Purified Talc	BP	4.000	–	Glidant
8.	Colloidal anhydrous silica	BP	2.000	–	Glidant
LUBRICATION					
9.	Stearic acid	BP	2.000	–	Lubricant
		Average Wt./Tab.	**180.000/Tablet**		

Note:

* Qty. to be calculated on basis of assay and LOD.

** Qty. to be compensate.

USP: United States Pharmacopoeia

BP: British Pharmacopoeia

IHS: In House specification

3. Pharmaceutical form

Dosage form: Uncoated tablet

Description: Light Yellow colored, round shaped, Flat Uncoated tablet having breakline on one side and plain on other side.

4. Clinical Particulars:

4.1 Therapeutic Indications:

Treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease.

4.2 Posology and method of administration:

Posology

The effect of tizanidine on spasticity is maximal within 2-3 hours of dosing and it has a relatively short duration of action. The timing and frequency of dosing should therefore be tailored to the individual, and tizanidine should be given in divided doses, up to 3-4 times daily, depending on the patient's needs. There is considerable variation in response between patients so careful titration is necessary. Care should be taken not to exceed the dose producing the desired therapeutic effect.

It is usual to start with a single dose of 2mg increasing by 2mg increments at no less than half-weekly intervals. The optimum therapeutic response is generally achieved with a daily dose of between 12 and 24mg, administered in 3 or 4 equally spaced doses. Single doses should not exceed 12mg. The total daily dose should not exceed 36 mg.

Elderly

Experience in the elderly is limited and use of tizanidine is not recommended unless the benefit of treatment clearly outweighs the risk. Pharmacokinetic data suggest that renal clearance in the elderly may in some cases be significantly decreased. Caution is therefore indicated when using tizanidine in elderly patients.

Pediatric population

Experience with tizanidine in patients under the age of 18 years is limited. Tizanidine is not recommended for use in this population.

Renal impairment

In patients with renal insufficiency (creatinine clearance < 25 ml/min) treatment should be started with 2mg once daily with slow titration to achieve the effective dose. Dosage increases should be in increments of no more than 2mg according to tolerability and effectiveness. If efficacy has to be improved, it is advisable to slowly increase the once-daily dose before increasing the frequency of administration. Renal function should be monitored as appropriate in these patients

Method of Administration:

Oral use.

4.3 Contraindications:

The use of tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver.Concomitant use of tizanidine with strong inhibitors of CYP1A2 such as fluvoxamine or ciprofloxacin is contraindicated.

4.4 Special warning and precaution for use:

CYP inhibitors Concomitant use of tizanidine with CYP1A2 inhibitors is not recommended.

Hypotension may occur during treatment with tizanidine and also as a result of drug interaction with CYP1A2 inhibitors and/or antihypertensive drugs. Severe manifestations of hypotension such as loss of consciousness and circulatory collapse have also been observed.

Withdrawal syndrome

Rebound hypertension and tachycardia have been observed after sudden withdrawal of tizanidine, when it had been used chronically, and/or in high daily dosages, and/or concomitantly with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident. Tizanidine should not be stopped abruptly, but rather gradually

Renal insufficiency

In patients with renal insufficiency (creatinine clearance < 25 mL/min), it is recommended to start treatment at 2 mg once daily. Dosage increases should be done in small steps according to tolerability and efficacy. If efficacy has to be improved, it is advisable to increase first the once daily dose before increasing the frequency of administration.

Cardiovascular, hepatic or renal disorders

Hepatic dysfunction

Since hepatic dysfunction has been reported in association with tizanidine but rarely at daily doses up to 12mg, is recommended that liver function tests should be monitored monthly for the first four months in patients receiving doses of 12mg and higher and in patients who develop clinical symptoms suggestive of hepatic dysfunction such as unexplained nausea, anorexia or tiredness. Treatment with tizanidine should be discontinued if serum levels of SGPT (serum glutamic-pyruvic transaminase) and/or SGOT (serum glutamic-oxaloacetic transaminase) are persistently above three times the upper limit of the normal range.

4.5 Interaction with other medicinal products and other forms of interaction:

CYP inhibitors: Concomitant administration of drugs known to inhibit the activity of CYP1A2 may increase the plasma levels of tizanidine. Concomitant use of tizanidine with fluvoxamine or ciprofloxacin, both CYP450 1A2 inhibitors in man, is contraindicated. Concomitant use of tizanidine with fluvoxamine or ciprofloxacin resulted in a 33-fold and 10-fold increase in tizanidine AUC, respectively. Clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor performance. Coadministration of tizanidine with other inhibitors of CYP1A2 such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine is not recommended.

Antihypertensives

As tizanidine may induce hypotension it may potentiate the effect of antihypertensive products, including diuretics, and caution should therefore be exercised in patients receiving blood

pressure lowering products. Caution should also be exercised when tizanidine is used concurrently with antihypertensive products, β-adrenoceptor blocking substances or digoxin as the combination may potentiate hypotension or bradycardia. In some patients rebound hypertension and tachycardia have been observed upon abrupt discontinuation of tizanidine when concomitantly used with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident.

Alcohol and sedatives may enhance the sedative action of tizanidine.

4.6 Pregnancy and Lactation:

Pregnancy

Animal studies indicate increased pre- and perinatal mortality at maternally toxic doses.

As there have been no controlled studies in pregnant women, however, it should not be used during pregnancy unless the benefit clearly outweighs the risk.

Breastfeeding

Although only small amounts of tizanidine are excreted in animal milk, tizanidine should not be taken by women who are breast-feeding.

4.7 Effects on the ability to drive and use machines:

None

4.8 Undesirable effects:

Hallucinations, insomnia, sleep disorders.

Somnolence, dizziness, Hepatitis, hepatic failure,

Headache, ataxia, dysarthria, Accommodation disorder, Bradycardia, tachycardia

Hypotension, rebound hypertension, Nausea, gastrointestinal disorder, Abdominal pain, vomiting, Muscular weakness.

4.9 Overdose:

Clinical experience is limited. In one case, where an adult patient ingested 400 mg tizanidine, recovery was uneventful. This patient received mannitol and furosemide

Symptoms

Nausea, vomiting, hypotension, bradycardia, QT prolongation, dizziness, miosis, respiratory distress, coma, restlessness, somnolence.

Treatment

General supportive measures are indicated and an attempt should be made to remove ingested substance from the gastro-intestinal tract using gastric lavage or by repeated administration of high doses of activated charcoal. The patient should be well hydrated as forced diuresis is expected to accelerate the elimination of tizanidine. Further treatment should be symptomatic.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Musculo-skeletal system; muscle relaxants; centrally acting agents; other centrally acting agents

ATC code: M03B X02

Tizanidine is a centrally acting skeletal muscle relaxant. Its principal site of action is the spinal cord, where the evidence suggests that, by stimulating presynaptic alpha2-receptors, it inhibits the release of excitatory aminoacids that stimulate N-methyl-D-aspartate (NMDA) receptors. Polysynaptic signal transmission at spinal interneuron level, which is responsible for excessive muscle tone, is thus inhibited and muscle tone reduced. Tizanidine has no direct effect on skeletal muscle, the neuromuscular junction or on monosynaptic spinal reflexes. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect.

In humans, tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.

5.2 Pharmacokinetic properties

Absorption

Tizanidine is rapidly absorbed, reaching peak plasma concentration in approximately 1 hour after dosing.

Distribution

Tizanidine is only about 30% bound to plasma proteins and, in animal studies, was found to readily cross the bloodbrain barrier. Mean steady-state volume of distribution (VSS) following i.v. administration is 2.6 L/kg.

Biotransformation

Although tizanidine is well absorbed, first pass metabolism limits plasma availability to 34% of that of an intravenous dose. Tizanidine undergoes rapid and extensive metabolism in the liver. Tizanidine is mainly metabolized by cytochrome P450 1A2 in vitro.

Elimination

The metabolites are primarily excreted via the renal route (approximately 70% of the administered dose) and appear to be inactive. Renal excretion of the parent compound is

approximately 53% after a single 5 mg dose and 66% after dosing with 4 mg three times daily. The elimination half-life of tizanidine from plasma is 2-4 hours in patients.

Effect of food

Concomitant food intake has no clinically significant influence on the pharmacokinetic profile of tizanidine tablets.

5.3 Pre-clinical Safety:

Not Applicable

6. Pharmaceutical Particulars:

6.1 List of Excipients:

- Micro crystalline cellulose BP
- Sodium starch glycolate BP
- Colour Quinoline Yellow IHS
- purified water BP
- Crospovidone BP
- Purified Talc BP
- Colloidal anhydrous silica BP
- Stearic acid BP

6.2 Incompatibilities: None

6.3 Shelf Life: 24 months.

6.4 Special Precautions for storage:

Store below 30° C in a dry place.
Protect from light.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container:

ALU-PVC Blister pack along with pack insert in a carton.

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder:

Ralphones Pharmaceutical Nigeria Limited

1. RALPHONES LANE , IKORODU ROAD, LAGOS STATE
Email: ralphonespharmaltd@yahoo.com , Tel.08037588238

RATNATRIS PHARMACEUTICALS PVT. LTD
SURVEY NO. 416,AT, INDRAD, TA. KADI, DIST. MEHSANA-382 715
GUJARAT, INDIA.

8. **Marketing Authorization Number:**
   NA

9. **Date of first Authorization /renewal of the authorization:**
   NA

10. **Date of revision of text:**
    NA